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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/584,996	06/11/2007	Robert Doblhofer	05281.0018	3945

22852 7590 03/19/2008

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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
03/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,996	ROBERT DOBLHOFER, ET AL.	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-11-07 & 1-3-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of inhibiting NOS release by the compounds of Formula (I) (page 28, *inter alia*), does not reasonably provide enablement for a method of treating a disorder associated with an increased NO level in a subject with compounds of Formula (I) (claims 32-39), where the disorder is selected from those characterized by pathological blood pressure decreases; inflammatory disorders; insulin-dependent diabetes mellitus; transplant rejection reactions; cardiovascular disorders; disorders of the nervous system/central nervous system; and kidney disorders (claim 40) where the subject is a mammal (claim 41) or a human (42). The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following reasons apply to this enablement rejection.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior

art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for hepatitis B surface antigen detection did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the compounds. The claims cover millions of 2,4-diamino-7,8-dihydropteridines of Formula (I).

(b) Scope of the diseases covered. The scope of disorders said to be controlled by inhibition of NOS include such diverse conditions as migraine, septic shock, neurodegenerative diseases, inflammation, cerebral ischemia, diabetes, meningitis, arteriosclerosis, wound healing, treatment of tumors, angiogenesis, *inter alia*. Claim 40 is directed to a method for treating a disorder selected from pathological blood pressure decreases; inflammatory disorders; insulin-dependent diabetes mellitus; transplant rejection reactions; cardiovascular disorders; disorders of the nervous system/central nervous system; and kidney disorders.

Disorders involving pathological blood pressure decreases include septic shock, a serious condition including low blood pressure and low blood flow that occurs with an overwhelming infection. Applicants fail to indicate whether the present

compounds function to alleviate the infection, the low blood pressure or the low blood flow. Weakened heart muscle can cause the heart to fail and reduce the amount of blood it pumps. A cause of weakened heart muscle is the death of a large portion of heart muscle due to a single, large heart attack or repeated smaller heart attacks. Other conditions that weaken the heart include medications toxic to the heart, infections of the heart muscle by viruses (myocarditis) and diseases of the heart's valves such as aortic stenosis.

Pericarditis, an inflammation of the pericardium, can cause fluid accumulation within the pericardium and compress the heart, restricting its ability to fill and pump blood. In pulmonary embolism, a blood clot breaks off from a deep vein thrombosis to travel to the heart and eventually the lung. A large blood clot can block the flow of blood into the left ventricle from the lungs and severely diminish blood returning to the heart. Pulmonary embolism is life–threatening. Bradycardia can decrease the amount of blood the heart pumps but does not always cause low blood pressure. Bradycardia can lead to low blood pressure, lightheadedness, dizziness, and fainting. Several common causes of bradycardia include sick sinus syndrome, heart block and drug toxicity. Sick sinus syndrome occurs when the heart electrical system of cannot generate signals fast enough to maintain normal heart rate. Heart block occurs when the tissues that transmit electrical current in the heart are damaged by heart attacks, degeneration from atherosclerosis or medications. Drugs such as digoxin or beta blockers for high blood pressure, can slow transmission of electricity in the heart chemically and can cause bradycardia and hypotension.

Tachycardia can cause low blood pressure, e.g., atrial fibrillation, a disorder of the heart characterized by rapid and irregular electrical discharges from the muscle of the heart causing the ventricles to contract irregularly and rapidly. Ventricular tachycardia also can produce low blood pressure and sometimes shock.

Disorders of the nervous system/central nervous system include such diverse diseases as multiple sclerosis, Parkinson's disease, Alzheimer's disease or Huntington's chorea. The claimed scope of nervous system/central nervous system includes the disorders listed by, for example, the Disorders Index of the National Institute of Neurological Disorders and Stroke, http://www.ninds.nih.gov/disorders/disorder_index.htm?css=print (NINDS Index) describing all disorders/diseases comprehended under this term.

Regarding inflammatory disorders, inflammation is a biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation includes such conditions as granulomatous inflammation, tuberculosis, leprosy, syphilis, fibrinous inflammation, purulent inflammation, including infection by pyogenic bacteria such as staphylococci, serous inflammation, commonly produced by mesothelial cells of serous membranes, and ulcerative inflammation, which can result in necrotic loss of tissue from the surface. Inflammation can also include allergic reactions, myopathies, immune system disorders, cancer, atherosclerosis, and ischaemic heart disease. Examples of other inflammation-associated disorders include asthma, autoimmune diseases, chronic inflammation, glomerulonephritis, hypersensitivities, inflammatory bowel diseases, pelvic inflammatory disease,

reperfusion injury, rheumatoid arthritis, transplant rejection, vasculitis, leukocyte defects, Chediak-Higashi syndrome and chronic granulomatous disease.

Adult (or Acute) Respiratory Distress Syndrome (ARDS) is severe inflammation in both lungs resulting in an inability of the lungs to function properly. ARDS is a devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. No specific therapies currently exist for ARDS patients. Treatment primarily involves supportive care in an intensive care unit , including use of a mechanical ventilator and supplemental oxygen to help patients breathe.

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive inflammatory disease of the airways that is characterized by a gradual loss of lung function. COPD includes chronic obstructive Bronchitis (which involves inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including Congenital Lobar Emphysema, Bullous Emphysema, Centrilobular Emphysema (Proximal acinar emphysema), Panacinar (panlobular), Distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, which is the genetic form of emphysema; patients often have both a form of bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air passageways, which can become clogged with mucus and have partially destroyed alveoli. There is no pharmaceutical treatment for COPD per se.

Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for the loss of lung function. Bronchodilators can expand passageways in the lungs, Corticosteroids can reduce inflammation and Antibiotics can ward off bacterial infections, but none of these treat the COPD itself.

Behçet's disease is a syndrome of unknown origin, but appears to be an autoimmune disorder. It is characterized primarily by inflammation of the blood vessels. Symptoms include a broad range of problems, which include mouth sores, genital sores, skin sores or lesions, meningoencephalitis, Uveitis, inflammation of the joints, thrombophlebitis, aneurysms, digestive tract ulceration (sometimes called Behçet's colitis)

Encephalitis is inflammation of the brain itself, often caused by a group of arboviruses. Treatment of encephalitis is largely supportive because no specific antiviral agents, except for that which works against herpes simplex virus, are available for therapy. Pancreatitis is inflammation of the pancreas and can arise from abdominal trauma, or the formation of gallstones that obstruct the common bile duct. It can be associated with excessive ingestion of alcohol; with disorders such as cystic fibrosis or Reye's syndrome; or with scorpion stings. Infectious causes include mycoplasmas, Epstein-Barr viruses, Coxsackie viruses, leptospirosis, hepatitis viruses, mumps, congenital German measles, Ascaris worms, and syphilis. The inflammation per se is generally not treatable. Treatment is usually supportive and consists of the management of pain and intravenous feeding.

Neuroretinitis is a type of inflammation of the retina and optic nerve of the eye ("optic neuritis"). It is often idiopathic. It frequently arises secondary to some kind of infection, such as Hepatitis B, HSV, EBV, influenza A, mumps, Coxsackie B, TB, salmonella, Lyme disease, syphilis, leptospirosis, Histoplasmosis, Toxoplasmosis, toxocara, Sarcoidosis and cat-scratch disease. Treatment is thus to the underlying cause. For example, diffuse unilateral subacute neuroretinitis (DUSN) arises from nematodes deep in the retina or in the subretinal space. Anthelminthic treatment is then used. When the origin is Toxoplasmosis, then anti-Toxoplasma medications such as Pyrimethamine. Vogt-Koyanagi-Harada syndrome (Harada's disease) is an acute inflammatory, immune-mediated disorder that can cause choroidal neovascularization, severe chorioretinal atrophy, and secondary glaucoma.

River blindness arises from inflammation of the eye caused by larvae (microfilaria) of the nematode *Onchocerca volvulus*, although the *Wolbachia* bacteria may be involved as well. Multifocal choroiditis and panuveitis (MCP) is a posterior chorioretinal inflammatory disease of unknown etiology

Cystic fibrosis (CF) is an inherited disease characterized by an abnormality in the glands that produce sweat and mucus. It is chronic, progressive, and is usually fatal. The basis for the problem with CF lies in an abnormal gene, which results in an atypical electrolyte transport system within the cells of the body. The abnormal transport system causes the cells in the respiratory system, especially the lungs, to absorb too much sodium and water. This causes the normal thin secretions in our lungs to become very thick and hard to remove. The high risk of infection in the

respiratory system leads to damage in the lungs, lung that do not work properly, and eventually death of the cells in the lungs. The most common causes for infection in the lungs are Staphylococcus aureus, Haemophilus influenza and Pseudomonas aeruginosa (PA). The disorder itself is largely untreatable.

Osgood-Schlatter disease is a common form of inflammation of the knee in active adolescents. It has no pharmaceutical treatment *per se*. Other inflammations of the knee include Sinding-Larsen-Johansson disease, Patellofemoral syndrome, and osteochondritis dissecans. Adhesive capsulitis is a type of inflammation of the shoulder. Its origin is usually unknown.

An inflammatory response is a normal body process and for good reason. A certain level of inflammatory response is needed to protect the body from invading organisms, especially bacteria, viruses, and parasites. An acute inflammatory response is needed to activate the healing process for burns, mediated by a range of MMPs. In sprains or other ligament injuries, some inflammatory response is needed initially to initiate repair of the damage. In mechanical wounds, some inflammatory response is required for satisfactory wound healing and indeed anti-inflammatory drugs such as cortisone can impair healing when administered at the time of wounding. In fact, inflammation is too important to be dependent on a single pathway and so inflammation can be initiated by numerous different systems, and generally, if one fails or is thwarted, another can do some or all of the job.

Kidney disorders include more than 100 disorders, diseases, and conditions can lead to progressive kidney destruction. Diabetes and high blood pressure are

common kidney failure causes. Diseases that affect the blood vessels, including diabetes, high blood pressure and atherosclerosis, can impair the kidneys. The urinary tract can become blocked, or obstructed, e.g., from a kidney stone, tumor, expanding uterus during pregnancy or enlarged prostate gland. Urinary tract infections, e.g., cystitis, can lead to more serious infections further up the urinary tract. Pyelonephritis is an infection of kidney tissue; most often, the result of cystitis that has spread to the kidney. Infections elsewhere in the body, including, e.g., streptococcal infections, impetigo or a bacterial infection in the heart can also be carried through the bloodstream to the kidney.

Diabetes and high blood pressure can lead to glomerular disease. An autoimmune disorder, e.g., systemic lupus erythematosus or Goodpasture syndrome, can be the cause. An attack on the glomerulus may also occur after a bacterial infection, e.g., strep infection, impetigo or a cardiac infection. Viruses, e.g., HIV virus, can also trigger glomerular disease.

Glomerulonephritis may subside in a few weeks, permanently reduce kidney function, or progress to end-stage kidney failure. Nephrotic syndrome may include complications, e.g., as blood clots and high cholesterol. Any situation involving severe blood loss or reduced blood flow may inhibit kidney function. Severe dehydration, some aortic and heart surgeries, severe infection in the blood or heart and severe heart failure exemplify events that can lead to sudden kidney problems.

Kidney cancers are of two main types. Wilms tumor occurs in young children and is often detected as a firm swelling in the belly. Renal cell carcinoma occurs in middle-aged to older adults. Bladder cancers are also common.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

   Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

   > The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

   Plant Genetic Systems N.V. v. DeKalb Genetics Corp., 65 USPQ2d 1452, 1456 (Fed.Cir. 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for the various conditions.

4. **State of the prior art:** Christopherson, et al., J. Clin. Invest., Vol. 100, No. 10, Nov. 1997, 2424-2429, discusses the relationship between NOS inhibition and neurodegenerative diseases (disorders of the nervous system/central nervous system), e.g., Parkinson's disease, but observing (pg. 2428, col. 1), "it remains less

clear whether long-term treatment [with NOS inhibitors] would be therapeutic for slowing developing neurodegenerative disorders."

Regarding a relationship between NOS inhibition and septic shock, a disorder characterized by pathological blood pressure decrease, Wolfe, et al., Ann. Pharmacother. 1995 Jan; 29(1): 36-46 (abst.) reported "use of NOS inhibitors to treat septic shock requires further studies to determine an appropriate dosing regimen and to determine the effects of these agents on morbidity and mortality."

In regard to a relationship between inhibition of NOS and transplant arteriosclerosis, a transplant rejection reaction, Akyurek, et al., Am. J. Path., Vol. 149, 1981-1990, 1996 (5 page abstract) observed that the role of NOS in the development of transplant arteriosclerosis (TA) is still unclear and that "[a]dditional studies are needed to confirm the modulatory mechanism of NO during the development of TA."

Regarding a relationship between NOS inhibition and angiogenesis, a cardiovascular disorder, Parenti, et al., FASEB. J. (April 27. 2001) 10.1096/fj.00-0503fje, reports:

> Our data demonstrate that upstream signaling leading to FGF-2 [fibroblast growth factor 2] up-regulation is controlled by the NOS pathway. Thus, as reported for other angiogenic peptides, the NOS pathway activation in endothelium sustains angiogenesis by priming endothelial cell in an autocrine/paracrine fashion. The existence of an autocrine loop within the capillary endothelium is thus reinforced by the fact that BK [bradykinin] /B1 [Lysdes-Arg^{9}-BK] receptor induces NOS activation and cGMP accumulation, both required to transduce FGF-2 up-regulation and postcapillary endothelial cell proliferation. **Nevertheless, characterization**

of molecular events at the nuclear level for the transcriptional control exerted by BK [bradykinin] remains to be solved.
(Emphasis added.)

The NIH Medline Plus website recognizes that treatment of arteriosclerosis, a cardiovascular disorder, focuses on relief of symptoms and improvement of circulation; http://www.nlm.nih.gov/medlineplus/ency/article/000170.htm#top, downloaded 02-24-2008. Applicants fail to identify what symptoms the claimed compounds alleviate. Prevention of arteriosclerosis consists in controlling obesity and high blood pressure and avoiding smoking, but Applicants fail to disclose how the claimed compounds assist in such inhibitory factors.

Ability of an agent that inhibits abnormal NOS activity to treat or ameliorate all diseases/conditions the present claims recite is open to further study and proof.

5. **Working Examples:** The specification working examples do not show treatment of all recited conditions/diseases.

6. **Skill of those in the art:** Many if not most diseases said to be treated by the claimed compounds, e.g., Parkinson's disease, a disorder of the nervous system/central nervous system, etc., are known as difficult to treat. At present no known drug can successfully prevent or reverse the course of many of these diseases, despite the fact that many drugs are said to inhibit abnormal NOS activity.

Christopherson, Wolfe, Akyurek, Parenti and the NIH Medline Plus website all support the position that the ability of an agent that inhibits abnormal NOS activity to treat all disorders that the present claims recite is open to further study and proof.

7. **Quantity of experimentation needed to make or use the invention.** Quantity of experimentation needed to make or use the invention, based on the content of the disclosure, would place an undue burden on one skilled in the pharmaceutical arts, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for the reasons stated above.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses. Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. The disclosure in this application is not sufficient to enable the instantly claimed methods based solely on disclosure of inhibition of NOS by compounds of Formula (I).

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

The above consideration clearly justifies that conclusion here and undue experimentation would be required to practice Applicants' invention. The

consideration of the above factors demonstrates that the present application does not sufficiently enable the present claims.

Claims 23-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for Formula I compounds, stereoisomeric and tautomeric forms and physiologically tolerated salts and esters thereof, does not reasonably provide enablement for their hydrates, or mixtures thereof in all ratios. The specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims, in embracing hydrates, are not enabled. The specification prophesizes hydrates, but the numerous examples presented all failed to produce a hydrate. The evidence of the specification is clear: These compounds do not possess the property of forming hydrates; there is no evidence that such hydrates even exist.

This is a circumstance where the "specification is evidence of its own inadequacy" (*In re Rainer*, 153 USPQ 802, 807). Hydrates cannot be simply willed into existence. *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 states:

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist ... the examples of the '881 patent do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The same circumstance appears true here: no evidence shows that hydrates of these compounds actually exist; if they did, they would have formed. Applicants must show making hydrates or limit the claims accordingly.

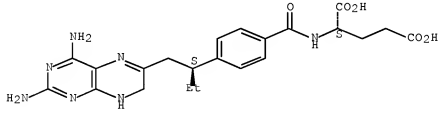
The recitation "mixtures thereof in all ratios" encompasses unsupported mixtures of claimed compounds and the recited forms; it should be singularized.

Rejections Under 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

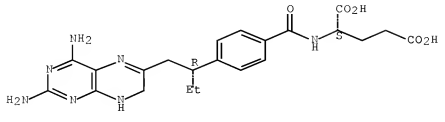
> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 23 and 31 are rejected under 35 USC 102(b) over DeGraw, et al., US 4746659, issued Jul. 16, 1987, describing 10-alkyl-10-deazaminopterins as anti-tumor agents. See the compounds and compositions of the claims. Note especially RN 102153-04-8, L-Glutamic acid, N-[4-[1-[(2,4-diamino-1,7-dihydro-6-pteridinyl)methyl]propyl]benzoyl]-, (S)-,



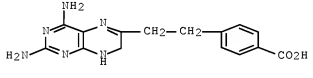
; and

RN 102153-05-9, L-Glutamic acid, N-[4-[1-[(2,4-diamino-1,7-dihydro-6-pteridinyl)methyl]propyl]benzoyl]-, (R)-,



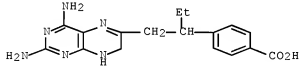
. Also see the compounds (col. 1, line 48- col. 3, line 26, *inter alia*) that DeGraw acknowledges to be known in the prior art having anti-tumor activity.

Claims 23 and 31 are rejected under 35 USC 102(b) over Nair, Journal of Organic Chemistry (1985), 50(11), 1879-84, describing RN 96056-44-9, Benzoic acid, 4-[2-(2,4-diamino-1,7-dihydro-6-pteridinyl)ethyl]-,



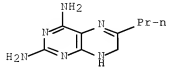
; and

RN 96056-45-0, 4-[1-[(2,4-diamino-1,7-dihydro-6-pteridinyl)methyl]propyl]- Benzoic acid,

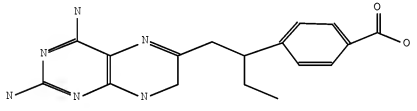


, as anti-tumor agents.

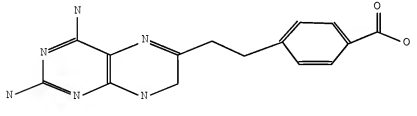
Claim 23 is rejected under 35 USC 102(b) over Taylor, et al., Journal of the American Chemical Society (1973), 95(19), 6413-18 (cited by Applicants), describing RN 50691-64-0, 2,4-Pteridinediamine, 1,7-dihydro-6-propyl-,



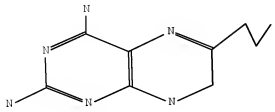
Claim 23 is rejected under 35 USC 102(b) over Beilstein Record 5633531, dated Feb. 12, 1993, describing 4-[1-(2,4-diamino-7,8-dihydro-pteridin-6-ylmethyl)-propyl]-benzoic acid,



Claim 23 is rejected under 35 USC 102(b) over Beilstein Record 5613739, Dated 1993/02/12, Describing 4-[2-(2,4-diamino-7,8-dihydro-pteridin-6-yl)-ethyl]-benzoic acid,



Claim 23 is rejected under 35 USC 102(b) over Beilstein Record 1117249, Dated 1988/11/29, 6-propyl-7,8-dihydro-pteridine-2,4-diamine,



Claim 23 is rejected under 35 USC 102(b) over each of the following, each dated Nov. 28, 1988, each cited by Applicants:

- Beilstein Registry No. 521731, 6-methyl-7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 525714, 6,8-dimethyl -7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 531116, 8-ethyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 532168, 8-isopropyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 551214, 8-benzyl-6-methyl-7,8-dihydro-pteridine-2,4-diamine;
- Beilstein Registry No. 598897, N-{4-[(2,4-diamino-7,8-dihydro-pteridin-6-ylmethyl)-methyl-amino]-benzoyl}-glutamic acid; and
- Beilstein Registry No. 599420, N-{4-[(2,4-diamino-8-methyl-7,8-dihydro-pteridin-6-ylmethyl)-methyl-amino]-benzoyl}-glutamic acid.

Claim 23 is rejected under 35 USC 102(b) over each of the following, each dated Aug. 28, 1992, each cited by Applicants:

- Beilstein Registry No. 5108955, 2,4-diamino-8-benzyl -7,8-dihydro-6,7,7-trimethylpteridine; and

- Beilstein Registry No. 5032074, 2,4-diamino-7,8-dihydro-6,7,7-trimethylpteridine.

Claim 23 is rejected under 35 USC 102(b) over Zimmerman, et al., J. Med. Chem. 1977, 20(9), 1213-15, cited by Applicants, describing 7,8-dihydro-6,7-bis(1-methylethyl)- 2,4-pteridinediamine.

Claim 23 is rejected under 35 USC 102(b) over Kwee, et al., Biochem. Biophys. Acta, 1973, 297(2), 285-96, cited by Applicants, describing 7,8-dihydro-6,7-dimethyl-2,4-pteridinediamine.

Claims 23, 24 and 31 are rejected under 35 USC 102(b) over Elion, US 3242178, issued Mar. 22, 1966 (cited by Applicants), describing 2,4-diamino-6-hydroxymethyl-7,8-dihydropteridine, found to inhibit biochemical synthesis of p-2-amino-4-hydroxypteridin-6-yl-methylamino-benzoylglutamic acid (folic acid).

Rejections Under 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

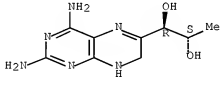
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 23, 27, 28, 31-33, 36, 37 and 40-42 are rejected under 35 USC 103(a) over Werner I, et al., EP 906913 A1, patented 19990407 (cited by Applicants), describing 1,2-Propanediol, 1-(2,4-diamino-1,7-dihydro-6-pteridinyl)-, (1R,2S)-,



, as an NO synthase inhibitor. The Werner I compounds (page 2, ¶ [0004], *inter alia*) render obvious lower alkyl homologs and position isomers thereof, encompassed by the present claims. The skilled chemist would be well motivated to prepare other compounds and their compositions homologous and isomeric with those of Werner I according to the procedures taught

therein with the expectation that such compounds would have the same activity. Thus, the skilled practitioner would also be motivated to use such homologous and isomeric compounds and their compositions in methods of treating a disorder associated with an increased nitric oxide level.

It would have been obvious to one of ordinary skill in the art at the time the present invention was made to modify the compounds of Werner I to prepare compounds homologous and isomeric therewith. One of ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous and isomeric compounds are expected to possess similar properties to the Werner I compound. It has been held that compounds that are structurally homologous and isomeric to prior art compounds are *prima facie* obvious, absent a showing of unexpected results.

> An obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.

In re Payne, 203 USPQ 245, 254 (CCPA 1979). See *In re Papesch*, 137 USPQ 43 (CCPA 1963) and *In re Dillon*, 16 USPQ2d 1897 (Fed.Cir. 1991) (discussed in MPEP § 2144) for an extensive case law review of obviousness based on close structural chemical compound similarity. See MPEP § 2144.08, ¶ II.A.4(c). Compounds which are homologs (compounds differing regularly by the successive addition or subtraction of the same chemical group, e.g., by -CH3 or lower alkyl groups) or position isomeric, as here, are generally of sufficiently close structural similarity that there is a presumed

expectation that such compounds possess similar properties. *In re Wilder*, 195 USPQ 426 (CCPA 1977).

Claims 23, 27, 28, 31-33, 36, 37 and 40-42 are rejected under 35 USC 103(a) over Werner II, US 5922713, issued Jul. 13, 2000 (cited by Applicants), describing pteridine compounds (col. 2, line 40 – col. 3, line 42, *inter alia*) for inhibition of nitric oxide synthase. See especially the compounds of Werner II in claims 10-13, *inter alia*. Note also the compounds of Table I (col. 1, lines 1-33, *inter alia*), that Werner II acknowledges to be known in the prior art that bind nitric oxide synthase. The Werner II compounds render obvious lower alkyl homologs and positions isomer thereof, encompassed by the present claims. The skilled chemist would be well motivated to prepare other compounds and their compositions homologous and isomeric with those of Werner II according to the procedures taught therein with the expectation that such compounds would have the same herbicidal activity. Thus, the skilled practitioner would also be motivated to use such homologous and isomeric compounds and their compositions in methods of treating a disorder associated with an increased nitric oxide level. See the discussion above of the obviousness of such closely structurally related compounds, their salts and compositions.

Obviousness Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 32-42 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as unpatentable over claims 20-42 of US SN 10549200. Although the conflicting claims are not identical, they are not patentably distinct from each other, because there is significant overlap between claims 20-42 of US SN 11389112 and the instant claims 32-42. Although the claims of US SN 11389112 state that they are directed to a method of treating a subject having an increased intracranial pressure, while the claims of the present application state that they are directed to a method of treating a disorder associated with an increased nitric oxide level, both sets of claims involve the same steps of administering 2,4-diamino-7,8-dihydropteridines that inhibit nitric oxide synthase. This obviousness-type double patenting rejection is provisional because the conflicting claims of neither application have in fact yet been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CECILIA M. JAISLE, J.D. whose telephone number is (571)272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner
Art Unit 1624

CECILIA M. JAISLE, J.D.
2/24/2008